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Safety and effectiveness of intravenous thrombolysis with recombinant tissue plasminogen activator in eighty years and older acute ischemic stroke patients

Y. CHEN, C.-H. LI, Y.-X. WANG, C.-H. ZHANG, Z. DONG, F.-F. ZHANG, J.-H. WANG, P.-L. ZHANG

Department of Neurology, Tianjin Huanhu Hospital, Tianjin Key Laboratory of Cerebral Vascular and Neurodegenerative Diseases, Tianjin, China

Abstract. – OBJECTIVE: To explore the safety and efficacy of intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rt-PA) in elderly (≥ 80 years old) acute ischemic stroke (AIS) patients.

PATIENTS AND METHODS: The clinical data of patients who were treated in Tianjin Huanhu Hospital from June 2012 to November 2013 were retrospectively analyzed; amongst them 404 patients had received IVT with rt-PA and 200 patients had not received IVT. Among ≥80 years' old patients, 204 had received IVT and 200 had not. And, the 404 patients who had received IVT, they were divided into two subgroups: elderly (≥ 80 years of age; n = 204) and controls (< 80 years old; n = 200). The incidence of intracranial hemorrhage (ICH) and symptomatic intracranial hemorrhage (sICH), case-fatality rate, and other prognostic indicators were compared.

RESULTS: Among all ≥80 years' old patients, the IVT subgroup had significantly superior good outcome rates than the non-IVT subgroup at 24-h and 3-month, along with significantly lower case-fatality rate. But for the patients those who had received IVT, the incidence of ICH and the 7-day case-fatality rate were not significantly increased in both the elderly and control subgroups. The 24-h and 3-month good outcome rates were not significantly different between these two subgroups as well.

CONCLUSIONS: IVT with rt-PA is a safe and effective treatment for ≥ 80 year's old AIS patients.

Key Words:
Elderly, 80 years, Acute ischemic stroke, Intravenous thrombolysis, Recombinant tissue plasminogen activator.

Introduction

According to the current American Heart Association/American Stroke Association (AHA/ASA) guidelines on the intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (rt-PA), ≥ 80 years of age is regarded as one of the relative exclusion criteria when applying IVT to patients who had suffered an acute ischemic stroke (AIS) 3-4.5 hours earlier[1]. Whether AIS patients older than 80 years can benefit from IVT still remains controversial. Some authors believe that patients ≥ 80 years of age generally have poor health conditions and therefore cannot tolerate IVT. It is also believed that patients of ≥ 80 years of age have particularly vulnerable cerebral vessels and therefore IVT can easily cause bleeding. However, research has also shown that compared to the younger patients, the case-fatality rate and bleeding risk were not significantly different in elderly patients, and therefore it was safe to apply the IVT with rt-PA in ≥ 80 year's old AIS patients. Thus, these ≥ 80 years old AIS patients could also benefit from IVT with rt-PA.

Patients and Methods

Patient's Clinical Data

The clinical data of patients who were treated in Tianjin Huanhu Hospital from June 2012 to November 2013 were retrospectively analyzed; among those 404 patients had received IVT with rt-PA (0.9 mg/kg) and 200 patients who were ≥ 80 years old had not received IVT. All ≥ 80 years old patients were divided into IVT subgroup (n = 204) and non-IVT subgroup (n = 200) based on their treatment. Among these 404 patients who had received IVT, they were divided into elderly subgroup (≥ 80 years) (n = 204) and control subgroup (< 80 years) (n = 200). The treatment was initiated on average 4.5 hours after the onset of the disease.

Corresponding Author: Pei-Lan Zhang, MD; e-mail: peilanzhng@sina.com

Inclusion/Exclusion Criteria

The inclusion/exclusion criteria were based on the 2013 AHA/ASA Guidelines for the early management of patients with acute ischemic stroke (within 4.5 hours)[1]. The inclusion/exclusion criteria for patients experiencing acute ischemic stroke eligible for the intervention of rt-PA thrombolysis were also applied three hours after the onset of the disease.

Inclusion criteria: (1) Diagnosis of acute ischemic stroke; (2) with measurable neurological deficits; (3) onset of symptoms < 3h before treatment; and d) age ≥ 18 years.

Exclusion criteria: (1) Significant head trauma or stroke within last three months; (2) with symptoms suggestive of subarachnoid hemorrhage; (3) unoppressed arterial puncture within past seven days; (4) history of intracranial hemorrhage; (5) intracranial tumors, arteriovenous malformations, aneurysms; recent intracranial or intraspinal surgery; (6) high blood pressure (systolic blood pressure > 185 mmHg or diastolic blood pressure > 110 mmHg); (7) active hemorrhage; acute hemorrhagic diathesis, including but not limited to platelet count < 100,000/mm^3(100×10^9/L); (8) administration of heparin in previous 48 hours with APTT above the upper normal limit (UNL); currently receiving oral anticoagulants; and INR > 1.5 or PT > 15 seconds; currently receiving the administration of direct thrombin or factor Xa inhibitors, with elevations of sensitive laboratory parameters (e.g., APTT, INR, platelet count and thrombin time [TT]; or factor Xa measurement if appropriate); (9) blood glucose concentration < 50 mg/dL (2.7 mmol/L); and (10) multiple lobar infarction as shown by intracranial CT scan (more than 1/3 of the cerebral hemispheres involved in the low density range).

Relative exclusion criteria: (1) Mild neurological symptoms or with rapid spontaneous remission; (2) pregnancy; (3) neurological deficits as the post-seizure sequelae; (4) recent major surgery or severe trauma within 14 days; (5) recent gastrointestinal or urinary tract hemorrhage within 21 days; and (6) myocardial infarction within three months.

Inclusion and Exclusion Criteria for Ischemic Stroke Patients who were Able to Receive rt-PA Treatment within 4.5 Hours After the Onset of Disease

Inclusion criteria for ischemic stroke patients who were able to receive rt-PA treatment within 4.5 hours after the onset of disease are; (1) Diagnosis of acute ischemic stroke; (2) with measurable neurological deficits; and (3) onset of symptoms 3-4.5 h before treatment.

Relative exclusion criteria for ischemic stroke patients who were able to receive rt-PA treatment within 4.5 hours after the onset of disease are; (1) > 80 years old; (2) severe stroke (with an NIHSS score of > 25); (3) oral administration of anticoagulants, regardless of the INR values; and (4) with history of both diabetes mellitus and ischemic stroke.

Methods

We compared IVT and non-IVT subgroups among ≥ 80 year's old AIS patients, as well as evaluated the elderly subgroup with the control subgroup of patients who had received IVT. The baseline data (e.g. age, gender, diabetes, hypertension, coronary heart disease, hyperlipidemia, atrial fibrillation, previous ischemic stroke, previous smoking history, blood glucose at admission, National Institutes of Health Stroke Scale (NIHSS) score at admission, time from disease onset to thrombolysis application, use of antiplatelet agents within 24 hours before the disease onset, and stroke etiology) and the outcomes after treatment (e.g. intracranial hemorrhage including symptomatic and non-symptomatic intracranial hemorrhage, hemorrhage in other sites, good outcome rate at 24-hour, 3-month, and 6-month as well as 7-day case-fatality rate) were analyzed.

Among these, the 24-hour good outcome rate was defined as "good" if the NIHSS score was decreased by ≥ 4 after 24 hours of treatment and as "poor" if less than 4. A "good" 3-month and 6-month prognosis is defined as 0-2 points of modified Rankin scores at month-3 and month-6, while poor prognosis is defined as 3-6 points of modified Rankin scores.

Statistical Analysis

Data were processed using SPSS 19.0 software. The measurement data were expressed as mean ± SD, and inter-group comparisons of mean values were implemented by using *t*-test with two independent samples. Categorical data were described by constituent ratio (%) or rate (%) and analyzed by chi-square test. $p < 0.05$ was considered significant. Fisher test was applied to compare the incidence of hemorrhage between the elderly and control subgrups.

Results

Comparison of IVT Efficacy in the Elderly Patients

The baseline data including the time from disease onset to thrombolysis and the common risk factors and hematologic examination of serum fibrinogen, albumin, globulin, total protein, ESR, cholesterol, triglycerides, lipoproteins were not significantly different for the IVT (n = 204) and non-IVT (n=200) subgroups (Table I). As shown in Table II, a significant difference was observed for the 24-hour, 3-month and 6-month good outcome rates between these two subgroups ($p < 0.05$). However, the 7-day case-fatality rate was not considerably different. Therefore, compared to the non-IVT subgroup, the IVT subgroup showed improved efficacy, enhanced long-term prognosis, and no increased case-fatality rate.

Comparison of the Safety of IVT in Patients

The baseline data including from the time of onset of disease to thrombolysis and the common risk factors and hematologic examination of serum fibrinogen, albumin, globulin, total protein, ESR, cholesterol, triglycerides, lipoproteins were not significantly different between the elderly (n = 204) and control (n = 200) subgroups (Table III). As shown in Table IV, after IVT, the case-fatality rate as well as the incidence of ICH (particularly the sICH) were not extensively increased in the elderly subgroup ($p > 0.05$ for all). The 24-hour, 3-month and 6-month good outcome rates were also not significantly different between these two subgroups ($p > 0.05$ for both). Therefore, these results show that the IVT safety was comparable between the elderly and control subgroups

Table I. Comparison of the baseline data of IVT and non-IVT subgroups among ≥80 year's old AIS patients.

	IVT group (n = 204)	Non-IVT group (n = 200)	*p*-value
Age (years; mean ± SD)	82.4±3.6	83.2±4.3	0.294
Men [n (%)]	141 (69)	132 (66)	0.481
Weight (kg, mean ± SD)	71.3±6.6	72.8±7.1	0.428
Previous disease history [n (%)]			
Diabetes mellitus [n (%)]	126 (62)	126 (63)	0.763
Hypertension [n (%)]	182 (89)	162 (81)	0.682
Hyperlipidemia [n (%)]	122 (60)	124 (62)	0.546
Smoking history [n (%)]	133 (65)	122 (61)	0.673
History of stroke and/or TIA [n (%)]	47 (23)	51 (26)	0.219
Atrial fibrillation [n (%)]	18 (9)	24 (12)	0.697
Coronary heart disease [n (%)]	43 (21)	47 (24)	0.467
Blood glucose at admission (mmol/L; mean ± SD)	6.8±2.7	6.9±3.1	0.554
NIHSS score at admission (mean ± SD)	7±3	7±4	0.936
Blood pressure before thrombolysis			
Systolic blood pressure [mmHg, mean ± SD]	141±14	145±17	0.373
Diastolic blood pressure [mmHg, mean ± SD]	84±10	86±9	0.615
Time from disease onset to thrombolysis (min, mean±SD)	212±28	226±37	0.732
Use of antiplatelet agents within 24 hours before treatment [n (%)]	39 (19)	42 (21)	0.864
Causes of stroke			
Large artery atherosclerosis [n (%)]	104 (51)	103 (52)	0.399
Cardioembolism [n (%)]	18 (9)	24 (12)	0.697
Small vessel occlusion [n (%)]	66 (32)	54 (27)	0.167
Others [n (%)]	16 (8)	19 (10)	0.671
Hematologic examination			
Serum fibrinogen (g/L; mean ± SD)	2.76±0.32	2.59±0.28	0.313
Albumin (g/L; mean ± SD)	45.1±6.2	46.7±6.5	0.415
Globulin (g/L; mean ± SD)	27.5±3.2	27.4±2.9	0.572
Total protein (g/L; mean ± SD)	72.6±9.4	74.1±9.6	0.247
ESR (mm/h; mean ± SD)	18.1±3.7	16.5±2.8	0.189
Cholesterol (mmol/L; mean ± SD)	5.02±0.64	5.11±0.59	0.656
Triglycerides (mmol/L; mean ± SD)	1.75±0.21	1.87±0.23	0.387
Lipoproteins (g/L; mean ± SD)	1.13±0.22	1.15±0.21	0.574

Note: TIA: transient ischemic attack; NIHSS: National Institutes of Health Stroke Scale, SD = standard deviation.

Table II. Comparison of the treatment outcomes for IVT and non-IVT subgroups among ≥80 year's old AIS patients.

	IVT group (n = 204)	Non-IVT group (n = 200)	*p*-value
Rate of good recovery [n (%)]	143 (70)	61 (31)	0.032
3-month good outcome rate [n (%)]	165 (81)	106 (53)	0.018
6-month good outcome rate [n (%)]	173 (85)	113 (57)	0.009
Case-fatality rate [n (%)]	4 (2)	9 (5)	0.046

Discussion

Cerebral infarction is the third killer disease worldwide. It has a high disability rate, and recently its annual incidence has shown an upward trend. Unfortunately age seems to be the most important risk factor. A remarkably higher incidence of cerebral infarction has been reported in people 55 years and older[3-6]. It has been found that cerebral infarction patients older than 65 years account for about 90% of the total number. More specifically, 50% of cerebral infarction patients are older than 70 years, and patients older than 85 years account for about 25% of the total

Table III. Comparison of the baseline data of elderly and control subgroups among patients who had received IVT.

	Elderly subgroup (n = 204)	Control subgroup (n = 200)	*p*-value
Age (years; mean ± SD)	82.4±3.6	65.9±7.4	0.000
Men [n (%)]	141 (69)	129 (65)	0.842
Weight (kg, mean ± SD)	71.3±6.6	69.7±7.3	0.325
Previous disease history			
Diabetes mellitus [n (%)]	126 (62)	116 (58)	0.364
Hypertension [n (%)]	182 (89)	167 (84)	0.157
Hyperlipidemia [n (%)]	122 (60)	104 (52)	0.126
Smoking history [n (%)]	133 (65)	133 (67)	0.882
History of stroke and/or TIA [n (%)]	47 (23)	58 (29)	0.187
Atrial fibrillation [n (%)]	18 (9)	23 (12)	0.368
Coronary heart disease [n (%)]	43 (21)	43 (22)	0.922
Blood glucose at admission (mmol/L; mean ± SD)	6.8±2.7	6.7±3.2	0.235
NIHSS score at admission (mean ± SD)	7±3	7±4	0.804
Blood pressure before thrombolysis			
Systolic blood pressure [mmHg, mean ± SD]	141±14	143±24	0.681
Diastolic blood pressure [mmHg, mean ± SD]	84±10	83±8	0.209
Time from disease onset to thrombolysis (min, mean ± SD)	212±28	220±35	0.294
Use of antiplatelet agents within 24 hours before treatment [n (%)]	39 (19)	44 (22)	0.457
Causes of stroke			
Large artery atherosclerosis [n (%)]	104 (51)	112 (56)	0.752
Cardioembolism [n (%)]	18 (9)	23 (12)	0.368
Small vessel occlusion [n (%)]	66 (32)	45 (22)	0.218
Others [n (%)]	16 (8)	20 (10)	0.904
Hematologic examination			
Serum fibrinogen (g/L; mean ± SD)	2.76±0.32	2.64±0.29	0.284
Albumin (g/L; mean ± SD)	45.1±6.2	48.3±6.7	0.326
Globulin (g/L; mean ± SD)	27.5±3.2	26.7±2.9	0.487
Total protein (g/L; mean ± SD)	72.6±9.4	75.0±10.3	0.125
ESR (mm/h; mean ± SD)	18.1±3.7	17.2±3.2	0.192
Cholesterol (mmol/L; mean ± SD)	5.02±0.64	4.86±0.61	0.537
Triglycerides (mmol/L; mean ± SD)	1.75±0.21	1.90±0.23	0.417
Lipoproteins (g/L; mean ± SD)	1.13±0.22	1.21±0.19	0.363

Note: TIA: transient ischemic attack; NIHSS: National Institutes of Health Stroke Scale, SD = standard deviation.

Table IV. Comparison of the outcome data of elderly and control subgroups among patients who had received IVT.

	Elderly (n = 204)	Control subgroup (n = 200)	*p*-value
Intracranial hemorrhage [n (%)]	8 (4)	6 (3)	0.667
Symptomatic intracranial hemorrhage [n (%)]	3 (1)	2 (1)	0.924
Non-symptomatic intracranial hemorrhage [n (%)]	5 (2)	4 (2)	0.381
Hemorrhage at other sites [n (%)]	20 (10)	23 (12)	0.208
Rate of good recovery [n (%)]	143 (70)	157 (79)	0.151
3-month good outcome rate [n (%)]	165 (81)	170 (85)	0.096
6-month good outcome rate [n (%)]	173 (85)	174 (87)	0.113
Case-fatality rate [n (%)]	4 (2)	2 (1)	0.107

number[7,8]. The world population is on an aging trend. There will be 55 million people aged 85 years and over worldwide by the year 2050[9]. In addition to its high incidence, the high mortality and disability rates are also of major concern. Currently, the IVT with rt-PA is the only thrombolytic therapy approved by the US FDA for AIS patients. However, the 2013 ASA/AHA guidelines on IVT listed the age of > 80 years as a relative exclusion criteria; thus, many elderly patients have no chance to receive IVT as a treatment for AIS[1]. In a time of global aging, the elderly patients, particularly those who are older than 80 years, should also have the right to benefit from IVT, which may reduce the AIS-associated disability and could lower the family and social burdens.

Until now very few clinical trials have explored the role of IVT in patients aged ≥ 80 years, and most studies, in particular large trials such as ECASS stage I, II, and III trials and ATLANTIS, excluded this age group. Such exclusion is based on the assumption that IVT is associated with cerebral hemorrhage in elderly patients. In addition, some studies have demonstrated that the efficacy of IVT remains unclear in patients 80 years of age and older[14]. However, in the NINDS study, the main predictors of sICH are the severity of stroke (based on NIHSS score) and the CT findings of early ischemia; age is not an independent predictor[11]. Therefore, rt-PA may be beneficial for patients in all age-groups. According to a case report, a 104-year-old patient benefited from IVT[15]. Meanwhile, IVT was found to be safe and effective in 11 patients 80 years of age and older[16]. According to the recently published IST-3 results among 1617 patients aged 80 or > 80 years, the survival rate was not significantly different for the treatment and control group, indicating that the IVT did not increase the case-fatality rate. It was also found that patients aged 80 or > 80 years benefited more from IVT than those younger than 80 years. Therefore, IVT conducted in the elderly patients did not weaken the efficacy of rt-PA[17].

Thus, further studies are required to confirm whether patients older than 80 years of age could benefit from IVT with rt-PA. As shown in our current study, among the elderly patients aged 80 or > 80 years, the IVT subgroup was significantly superior to the non-IVT subgroup in terms of 24-hour, 3-month and 6-month good outcome rates. Three months later, and more particularly six months later, remarkable efficacy was found in the IVT subgroup. Meanwhile, the 3-month and 6-month good outcome rates were not significantly different between the elderly and control subgroups after the IVT, indicating that the elderly patients can benefit with the same good efficacy of IVT as the younger populations. Consequently, it is reasonable to conclude that rt-PA is effective in treating elderly (≥ 80 years of age) AIS patients. The IVT with rt-PA can not only improve the symptoms faster in the elderly AIS patients but also facilitate the long-term recovery of neurological disorders.

We also found that the incidence of sICH and case-fatality rate were not considerably different between the elderly and control subgroups among patients who had received IVT[18], suggesting that the use of rt-PA in the elderly patients did not increase the risk of bleeding and the case-fatality rate in and therefore it is relatively safe to use in the elderly patients as well.

Therefore, as shown in our study, the elderly patients aged 80 or > 80 years, when carefully selected, can also benefit from IVT with rt-PA, which can reduce the disability rate of these elderly AIS patients, lower the family burden, and thus exert significant social benefits.

Since IVT has not been widely applied across China, this study was conducted only in one center. We hope that in the future the IVT for AIS patients will be promoted in clinical settings, which can increase the rate of IVT among Chinese population, so that the multi-center large-sample studies become possible. Finally, the evaluation of the 6-month efficacy of IVT is far from enough and in the future, we should continue the follow-up of these treated patients, to identify the long-term efficacy of IVT in these elderly patients.

In summary, our current study further demonstrated the safety and effectiveness of IVT with rt-PA in AIS patients aged 80 or > 80 years. We hope that more elderly patients, particularly those with good general health conditions (e.g. without the dysfunction of liver, kidney, heart, or lung and a history of cerebral infarction before the onset of AIS), can profit from the enormous benefits of IVT.

Conclusions

Present data show that the IVT with rt-PA is a safe and effective treatment for elderly (> 80 years old) AIS patients.

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Findings

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Conflict of Interest

The Authors declare that they have no conflict of interests.

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